

## CORRESPONDENCE

### Letters to the Editor

## Drug Therapy for Hypercholesterolemia Time to End the Double Standard

In his Viewpoint paper regarding atherosclerosis screening, Shah (1) decries the “double standard” of requiring proof of clinical benefit for imaging studies but not for clinical risk scores. However, a far more troublesome double standard relates to the treatment of hypercholesterolemia versus the treatment of other modifiable cardiovascular risk factors. The initiation of drug therapy for hypertension, diabetes, and cigarette smoking is not dependent on any calculation of the estimated risk of developing a hard cardiovascular end point within an arbitrary time period. Those with hypertension or diabetes who do not reach their treatment goals with lifestyle modification alone or those who are unable to quit smoking “cold turkey” are appropriately treated with drug therapy. In fact, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) explicitly states that it “does not stratify hypertensive individuals by the presence or absence of risk factors . . . in order to make different treatment recommendations . . . JNC 7 suggests that all people with hypertension . . . be treated” (2). Among the modifiable cardiovascular risk factors, only hypercholesterolemia requires anything other than the presence of the risk factor itself to prompt treatment.

Shah (1) explicitly raises this issue himself, but dismisses the unconditional treatment of hypercholesterolemia with statins because of concerns regarding cost, need for lifetime use, and intolerance. However, these concerns are certainly no different than those associated with drug treatment for hypertension or diabetes, issues not addressed by Shah (1). Moreover, statins are among the safest medications ever introduced (3) and are generally no more expensive or risky than many widely prescribed antihypertensive and antidiabetic drugs. Most remarkably, Shah (1) is not in favor of unconditional treatment of hypercholesterolemia, in part because statin therapy “only addresses about 30% to 50% of the risk.” It is difficult to understand why a reduction of risk of this magnitude for a condition that accounts for nearly one-third of all deaths worldwide would represent anything other than a powerful endorsement of treatment. It is time to embrace the unconditional treatment of hypercholesterolemia and bring lipid treatment in line with the well-established treatment paradigms for other cardiovascular risk factors.

**\*Howard A. Cooper, MD**

\*Coronary Care Unit  
Washington Hospital Center  
110 Irving Street NW  
Suite NA-1103  
Washington, DC 20010  
E-mail: [howard.a.cooper@medstar.net](mailto:howard.a.cooper@medstar.net)

## REFERENCES

1. Shah PK. Screening asymptomatic subjects for subclinical atherosclerosis: can we, does it matter, and should we? *J Am Coll Cardiol* 2010;56:98–105.
2. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289:2560–72.
3. Armitage J. The safety of statins in clinical practice. *Lancet* 2007;370:1781–90.

## Reply

I appreciate the comments by Dr. Cooper regarding my Viewpoint paper (1). I fully concur with Dr. Cooper that 30% to 50% relative cardiovascular risk reduction with statins is a highly clinically worthwhile benefit, but I beg to differ that unconditional treatment of everyone without known atherothrombotic cardiovascular disease and hyperlipidemia with a statin is appropriate. It is an established fact that atherothrombotic cardiovascular disease does not develop in a significant proportion of subjects with hyperlipidemia, and, conversely, a significant proportion of subjects with atherothrombotic cardiovascular disease do not have hyperlipidemia; in fact, the real definition of what constitutes hyperlipidemia is itself unclear. If the goal of using a statin is to reduce atherothrombotic cardiovascular events, then it is unrealistic to expect those patients without significant atherosclerosis to benefit from statin therapy even if they have hyperlipidemia; in such subjects, one can only expect side effects and extra costs associated with statin use. Fortunately, we now have the ability to identify subclinical atherosclerosis in 2 major vascular beds noninvasively so that those patients without atherosclerosis can be observed and reassessed while adopting a healthy lifestyle without resorting to statin therapy. Because hypertension has adverse effects beyond simply an association with atherosclerosis, such as increased risk of stroke, especially hemorrhagic stroke, renal failure, congestive heart failure, and aortic aneurysm formation, one cannot equate hyperlipidemia management with hypertension management. Similarly, smoking-associated health risk includes lung disease, cancer, and thrombotic cardiovascular events even with minimal atherosclerosis; smoking cessation is advisable for every smoker regardless of other risk factors. In this day and age, where we are headed toward the concept of “personalized medicine” (matching treatment to underlying risk and disease phenotype rather than a “one size fits all” strategy, which has been the prevailing paradigm), the approach outlined in my Viewpoint paper is a step in that direction.

**\*Prediman K. Shah, MD**

\*Cedars Sinai Heart Institute, Los Angeles  
Suite 5513  
8700 Beverly Boulevard  
Los Angeles, California 90048  
E-mail: [shahp@cshs.org](mailto:shahp@cshs.org)

## REFERENCE

1. Shah PK. Screening asymptomatic subjects for subclinical atherosclerosis: can we, does it matter, and should we? *J Am Coll Cardiol* 2010; 56:98–105.

## Misinterpretation of Prostate Cancer Data

In a recent issue of the *Journal*, Lauer (1) suggested that the lack of effect of prostate-specific antigen (PSA) screening for prostate cancer is an important reason to be cautious about screening for subclinical coronary artery disease. Unfortunately, his argument might be fallacious. First, he states that prostate cancer death rates have not declined, despite widespread screening. Quite the contrary is true. Death rates due to prostate cancer have substantially declined in the U.S. from 39.2 to 23.6/100,000 from 1992 to 2006 (2–4). This is an age-adjusted decline of approximately 4%/year. From 1991 to 2004, prostate cancer mortality has declined much more rapidly in the U.S. with the frequent use of PSA testing than in the United Kingdom, where there is less screening (4.2%/year in the U.S. vs. 1.1%/year in the United Kingdom) (5).

Second, he points to the recent report of the PLCO (Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial) that failed to document benefit of prostate cancer screening with PSA (6). Unfortunately, the PLCO trial was contaminated by high screening rates in the comparison group and a lack of control for therapies for prostate cancer. It is estimated that probably 50% of men 50 years of age and older in the U.S. have a PSA test. Most recently, PSA testing was evaluated in a population that was previously unexposed to PSA testing. A randomized trial of 20,000 men in Göteborg, Sweden, 50 to 64 years of age at entry were followed an average of 14 years (7). The reduction of prostate cancer deaths was 40% (range 0.17 to 64) in the PSA screening versus control group,  $p = 0.002$ . Approximately 293 men needed to be screened and 12 needed to be diagnosed to prevent 1 prostate cancer death—44 deaths in the intervention versus 78 in the control group. The effect of PSA testing on reducing mortality in this study was of similar magnitude as mammography screening for breast cancer.

A trial to evaluate screening of asymptomatic individuals for the prevention of subsequent clinical coronary artery disease events (i.e., screening asymptomatic individuals with coronary calcium detection) is impractical. The technology is widely available; its prognostic implications are well-published; and preventive therapies such as lipid lowering, antihypertensive therapy, and lifestyle modifications are now accessible and affordable. Such a trial, like the PLCO trial, will be contaminated by crossovers, use or lack of use of statins and other effective therapies, and poor compliance with dietary and pharmacological therapies. The trial of hard end points (i.e., coronary heart disease [CHD] deaths or myocardial infarction), will require long follow-up because of the early stage of incubation of atherosclerosis in which these individuals will be detected. Do we really need to prove that lipid lowering is effective in individuals with atherosclerosis for reducing CHD mortality? Do we need to waste another 7 to 10 years and millions of dollars of valuable research funds? The key is maximizing the use of proven effective preventive pharmacological and nonpharmacologi-

cal therapies by targeting the population most likely to benefit from them and thereby substantially reducing CHD incidence, mortality, and costs of health care.

**\*Lewis H. Kuller, MD, PhD**  
**Daniel Edmundowicz, MD, MS**

\*Department of Epidemiology  
University of Pittsburgh, GSPH  
130 North Bellefield Avenue  
Room 550  
Pittsburgh, Pennsylvania 15213  
E-mail: kullerl@edc.pitt.edu

doi:10.1016/j.jacc.2010.08.615

## REFERENCES

1. Lauer MS. Screening for asymptomatic subjects for subclinical atherosclerosis: not so obvious. *J Am Coll Cardiol* 2010;56:106–8.
2. Hughes V. Markers of dispute. *Nat Med* 2009;15:1339–43.
3. Kinsey T, Jemal A, Liff J, Ward E, Thun M. Secular trends in mortality from common cancers in the United States by educational attainment, 1993–2001. *J Natl Cancer Inst* 2008;100:1003–12.
4. DeLancey JOL, Thun MJ, Jemal A, Ward EM. Recent trends in black-white disparities in cancer mortality. *Cancer Epidemiol Biomarkers Prevention* 2008;17:2908–12.
5. Collin SM, Martin RM, Metcalfe C, et al. Prostate-cancer mortality in the USA and UK in 1975–2004: an ecology study. *Lancet Oncol* 2008;9:445–52.
6. Andriole GL, Crawford ED, Grubb RL III, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360:1310–9.
7. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomized population-based prostate cancer screening trial. *Lancet Oncol* 2010;11:725–32.

### Reply

In their thoughtful letter, Drs. Kuller and Edmundowicz challenge my call for randomized trials of coronary artery screening (1). They cite U.S./United Kingdom ecological data demonstrating public health benefits from prostate-specific antigen (PSA) screening (2) and then cite a just-published randomized trial that found reduced mortality (3). They argue that, in our current environment, it is impractical to execute trials, and even so, they are unnecessary: we already know lipid-lowering therapy works.

Numerous authorities have cited the limitations of observational analyses of screening; these include lead- and length-time bias, misattribution bias, and overdiagnosis. Even Collin et al. (2), who wrote the positive ecological study that Kuller and Edmundowicz cite, conclude their report stating, “We can only continue to speculate about the relative contributions of differences in detection and treatment or the relative balance of benefits and harms, until the publication of findings from trials provides the robust evidence that is so eagerly awaited.” I agree!

Prostate cancer kills far less often than coronary artery disease, yet academic leaders have completed large-scale trials. Two trials that enrolled approximately 250,000 patients showed little or no benefit and much overdiagnosis, whereas 1 trial an order of magnitude smaller suggests benefit in some patients (3). Academic leaders have performed screening trials for other less common diseases, including breast cancer, lung cancer, and aortic aneurysm. Surely we can execute a screening trial for coronary disease, the nation’s leading cause of death.